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EXAMINER	
CARTER, KENDRA D	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
07/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,929	MERCEP ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1 (in part) -15, are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = CH_2 , classified in class 514, subclass 366 and 765, and class 548 subclass 149 for example.

II. Claims 1 (in part) -15, are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = O, classified in class 514, subclass 366 and 450, and class 548 and 149 subclass.

III. Claims 1 (in part) -15, are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other

neurotransmitter comprising administering a compound of formula I, wherein X = S, S=O, or $(S=O)_2$, classified in class 514, subclass 366 and 431 and class 548 subclass 149 for example.

IV. Claims 1 (in part) -15, are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = NR^a, classified in class 514, subclass 215 and 366, and class 548 and subclass 149 for example.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I to IV and are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions have different compounds. Group I comprises a seven membered carbocyclic group, Group II comprises a seven membered oxygen heterocycle, Group II comprises a seven membered sulfur heterocycle, and Group IV comprises a seven membered nitrogen heterocycle.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election

shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Claims 1-15 are generic to the following disclosed patentably distinct species: a compound of formula I and a disease, damage or disorder. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at

the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

During a telephone conversation with Attorney Scott Young on June 16, 2009 a provisional election was made without traverse to prosecute the invention of Group III, claims 1-15. The species of depression for the disease, damage or disorder was elected, and the species where in X is S, Y and Z are H, R1 is formula A, wherein m is 1, n is 2, Q_1 is oxygen, Q_2 is C_{y1y2}, y1 and y2 are each H and R^3 and R^4 are each CH_3 . Affirmation of this election must be made by applicant in replying to this Office action.

Claim 1, wherein X = CH_2, O, or NR^a, is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Since the Examiner was unable to find art teaching the elected compound treating depression, the compounds of formula 1, X = S, S=O, or $(S=O)_2$, and all central nervous system diseases, damage or disorders were examined on the merits.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1-9, 11-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mercep et al. (WO 03/099827 A1) in view of Sheth et al. (US 4,867,979).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing

that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Mercep et al. teach that the Applicant's compound have anti-inflammatory action (see abstract; page 4-9 and 23, example 1).

Mercep et al. does not teach that the compounds treat CNS damage, disease, or disorder in claims 1 and 11 through any of the mechanistic pathways disclosed in claims 1 and 2-9.

Sheth et al. teach that anti-inflammatory drugs are used to treat diarrhea (i.e. gastrointestinal disorder; CNS damage; see abstract; addresses claims 1 and 11).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine Mercep et al. and the treatment of a CNS damage because Mercep et al. teaches that the compounds have anti-inflammatory activity and Sheth et al. teach that anti-inflammatory drugs are used to treat diarrhea (i.e. gastrointestinal disorder; CNS damage; see abstract; addresses claims 1 and 11). Thus, one would reasonable expect that the anti-inflammatory agents of Mercep et al. would treat diarrhea.

In regards to the mechanistic pathways disclosed in claims 1 and 2-9, it is considered that the compounds act in this manner because one can not separate the properties from the compound. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case or either anticipation or obviousness has been established. Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). "Products of identical chemical composition can not have mutually exclusive properties." Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F. 2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1) Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula I wherein X = S, S=O, or $(S=O)_2$ having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, does not reasonably provide enablement for treating <u>any</u> disease damage or disorder of the central nervous system with <u>any</u> compound of formula I wherein X = S, S=O, or $(S=O)_2$.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = S, S=O, or $(S=O)_2$. The instant specification fails to provide information that would allow the skilled artisan to <u>fully</u> practice the instant invention <u>without undue experimentation</u>. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation.

Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering to a subject in need thereof a compound of formula I…."

(2) The breadth of the claims:

Claims 1-15 embraces and reads on treating <u>any</u> disease, damage or disorder of the central nervous system associated with a disorder of neurochemical equilbirum of a bigenic amine or other neurotransmitter with <u>any</u> compound of formula I, wherein X = S, S=O, or $(S=O)_2$. The specification <u>does not</u> enable the treatment of <u>any</u> central nervous system disease, damage or disorder with <u>any or all</u> of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$.

(3) The state of the prior art:

The state of the art regarding effectively treating any disease, damage or disorder of the central nervous system with any of the compounds of formula I is very low. For instance, Wikstrom et al. (US 5,288,748) teach that the compounds of formula I, which bind to 5-HT_{1A} (serotonin), D2 (dopamine) and NA alpha-2 (noradrenaline receptors treat depression (see columns 7 and 8 in its entirety and claims 15 and 16). On the other hand, Williamson et al. (European Journal of Pharmacology, 1997, vol. 328, pp. 61-64) teach the treatment of a migraine with the 5-$HT_{1B/1D}$ receptor agonist rizatriptan (see title; page 61, column 2, line 15-17). Kast (Support Care Cancer, 2001, vol. 9, pp. 469-470) teaches that mirtazapine treats nausea through binding to the 5HT3 receptor, treats insomnia by antagonizing the 5HT2 receptor, and treats depression (see abstract). Thus, the compounds presented above do not treat all central nervous system disorder just because they bind to a 5HT receptor.

(4) The predictability or unpredictability of the art:

The predictability of treating any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$ is relatively low. Therefore, to one skilled in the art, treating any central nervous system disease, damage or disorder is unpredictable. In other words, just because there are potential therapeutic targets in binding to the 5-HT2A receptor, effective treatment has yet to be completely established. Therefore, because there is a "potential", treating central nervous disorders, damage or diseases, it is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Wikstrom et al., Williamson et al. and Kast.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to treating any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$ is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that treating any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. Particularly, the specification teaches that dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine has a binding affinity to 5-HT_{2a} and 5-HT_{2C} (see page 28, lines 6-7). The specification also teaches that "compounds" or “substance” reduced the immobility of animals (see page 29, paragraph 4 and page 30, paragraph 2), reduced amphetamine-induced hyperlocomotion in animals (see page 30, last paragraph), reduced the effects of m-CPP, (see page 31, paragraph 3), reduced the period of agitation, convulsions and tremors in animals (see page 32, paragraph 3). The specification does not provide any of the specific compounds which exhibit these

effects. Due to the numerous compounds that could have been tested, as evidenced by the restriction requirement, it is not clear if compounds wherein X = S, S=O, or $(S=O)_2$ exhibited effective treatment.

(7) The quantity of experimentation necessary:

The instant claims read on treating any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. As discussed above the specification fails to provide any support for treating any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every one of compounds as claimed, or at least a subset that is sufficiently representative of the compounds, to determine treatment efficacy for each condition. For example, to test for treatment of the disease, a particular compound having the activity to effect the equilibrium of a biogenic amine or other neurotransmitters, such as one of those corresponding to formula I, would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration) would also have to be selected. If efficacy of the drug did not result, the dosage regime would have to be varied, for example by changing the dosage amount or route of administration, until efficacy was achieved. If no animal model of a condition is available for testing, then

toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the treatment of the condition was shown with the particular compound, then another compound having the same activity would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compounds as claimed for treating central nervous order disorders, the process would have to be repeated. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each compound having the above activity for the treatment of that particular disease, damage or disorder, in order to be able to fully carry out the invention commensurate in scope with the claims.

Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for a compound of formula I, wherein X = S, S=O, or $(S=O)_2$. having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, but not for <u>any</u> compound of formula I wherein X = S, S=O, or $(S=O)_2$ to treat <u>any</u> central nervous system disease, disorder or damage.

2) Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula I wherein X = S, S=O, or $(S=O)_2$ having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, does not reasonably provide enablement for preventing any disease damage or disorder of the central nervous system.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = S, S=O, or $(S=O)_2$. The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering to a subject in need thereof a compound of formula I…."

(2) The breadth of the claims:

Claims 1-15 embraces and reads on preventing any disease, damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter with any compound of formula I, wherein X = S, S=O, or $(S=O)_2$. The specification defines treatment as preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition (see page 17, paragraph 3). The specification does not enable the prevention of any central nervous system disease, damage or disorder with any or all of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$.

(3) The state of the prior art:

The state of the art regarding effectively preventing any disease, damage or disorder of the central nervous system with any of the compounds of formula I is very low. For instance, Wikstrom et al. (US 5,288,748) teach that the compounds of formula I, which bind to 5-HT_{1A} (serotonin), D2 (dopamine) and NA alpha-2 (noradrenaline receptors treat depression (see columns 7 and 8 in its entirety and claims 15 and 16). On the other hand, Williamson et al. (European Journal of Pharmacology, 1997, vol. 328, pp. 61-64) teach the treatment of a migraine with the 5-$HT_{1B/1D}$ receptor agonist rizatriptan (see title; page 61, column 2, line 15-17). Kast (Support Care Cancer, 2001, vol. 9, pp. 469-470) teaches that mirtazapine treats nausea through binding to the 5HT3 receptor, treats insomnia by antagonizing the 5HT2 receptor, and treats depression (see abstract). Thus, the compounds presented do not prevent central nervous system disorder just because they bind to a 5HT receptor.

(4) The predictability or unpredictability of the art:

The predictability of preventing any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$ is relatively low. Therefore, to one skilled in the art, preventing any central nervous system disease, damage or disorder is unpredictable. In other words, just because there are potential therapeutic targets in binding to the 5-HT2A receptor, effective prevention has yet to be completely established. Therefore, because there is a "potential", prevention central nervous disorders, damage or diseases, it is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Wikstrom et al., Williamson et al. and Kast.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to preventing any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$ is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that prevent any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. Particularly, the specification teaches that dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine has a binding affinity to 5-HT_{2a} and 5-HT_{2C} (see page 28, lines 6-7). The specification also teaches that "compounds" or “substance” reduced the immobility of animals (see page 29, paragraph 4 and page 30, paragraph 2), reduced amphetamine-induced hyperlocomotion in animals (see page 30, last paragraph), reduced the effects of m-CPP, (see page 31, paragraph 3), reduced the period of agitation, convulsions and tremors in animals (see page 32, paragraph 3).

The specification does not provide any of the specific compounds which exhibit these effects. Due to the numerous compounds that could have been tested, as evidenced by the restriction requirement, it is not clear if compounds wherein X = S, S=O, or $(S=O)_2$ exhibited effective treatment.

(7) The quantity of experimentation necessary:

The instant claims read on preventing any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. As discussed above the specification fails to provide any support for preventing any central nervous system disease, damage or disorder with any of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every one of compounds as claimed, or at least a subset that is sufficiently representative of the compounds, to determine prevention efficacy for each condition. For example, to test for prevention of the disease, a particular compound having the activity to effect the equilibrium of a biogenic amine or other neurotransmitters, such as one of those corresponding to formula I, would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration) would also have to be selected and monitored for lengths of time to make sure that the disease never developed. If efficacy of the drug did not result, the dosage regime would have to be

varied, for example by changing the dosage amount or route of administration, until efficacy was achieved. Toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the prevention of the condition was shown with the particular compound, then another compound having the same activity would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compounds as claimed for preventing central nervous order disorders, the process would have to be repeated. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each compound having the above activity for the prevention of that particular disease, damage or disorder, in order to be able to fully carry out the invention commensurate in scope with the claims.

Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for the compound dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, but not for the prevention of any central nervous system disease, disorder or damage.

3) Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compound of formula I wherein X = S, S=O, or $(S=O)_2$ having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, does not reasonably provide enablement for any compound of formula I to regulate the synthesis, storage, release, metabolism, reabsorption or receptor binding of any biogenic amine or any neurotransmitter.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = S, S=O, or $(S=O)_2$. The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering to a subject in need thereof a compound of formula I…." Claim 4 is drawn to the "method of claim 1 wherein the compound of formula I regulates the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of a biogenic amine or neurotransmitter." Claim 5 is drawn to the "method of claim 4, wherein the compound of formula I binds to a receptor or a biogenic amine.

(2) The breadth of the claims:

Claims 4 and 5 embrace and read on regulating the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of <u>any</u> biogenic amine or <u>any</u> neurotransmitter with the compound of formula I, wherein X = S, S=O, or $(S=O)_{2,}$. The specification <u>does not</u> enable <u>all</u> (or a good subset) of the compounds of formula I, wherein X = S, S=O, or $(S=O)_{2,}$ the activity of regulating the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of <u>any</u> biogenic amine or neurotransmitter.

(3) The state of the prior art:

The state of the art regarding regulating the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of a biogenic amine or neurotransmitter with any solvate of the compound of formula I, wherein X = S, S=O, or $(S=O)_{2,}$ is very low. For instance, Wikstrom et al. (US 5,288,748) teach that the compounds of formula I, which bind to 5-HT_{1A} (serotonin), D2 (dopamine) and NA alpha-2 (noradrenaline receptors treat depression (see columns 7 and 8 in its entirety and claims 15 and 16). Particularly, compounds of the same core structure or even different diastereomers of the same compound have different if any activity towards the synthesis of DA and 5HT at the serotonin, dopamine and noradrenaline receptors (see Table 1). For instance compound (+)13a and (-)13a both showed activity at the D2 and 5HT1A receptor, but (-)13a did not effect the synthesis of DA or 5-HT. Thus, it can not be expected that all compounds with a similar core structure will have the same activity. Further, it can not be expected that just because a compound effects the synthesis of a biogenic amine does not mean that it will be effective in treating the disease or disorder. Kelly (Neurosciences, 1995, vol. 7, pp. 371-373) teaches that 5-Ht's have different roles in the central nervous system (see title). The operational properties of the 5-HT receptor on the neurons is determined by the receptor subtype, in which 5-HT has several (see page 372, column 1, paragraph 2, lines 1-15; and page 371, column 2, serotonin receptor family).

(4) The predictability or unpredictability of the art:

The predictability of regulating the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of a biogenic amine or neurotransmitter with any compound of formula I, wherein X = S, S=O, or $(S=O)_2$, is relatively low. Therefore, to one skilled in the art, treating any central nervous system disease, damage or disorder is unpredictable. In other words, just because there are potential to regulate the synthesis, storage, release, metabolism, reabsorbtion or receptor binding of a biogenic amine or neurotransmitter, effective activity has yet to be completely established. Therefore, because there is a "potential", it is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Wikstrom et al. and Kelly.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to any compound of formula I wherein X = S, S=O, or $(S=O)_2$ having the ability to regulate the synthesis, storage, release, metabolism, reabsorption or receptor binding of any biogenic amine or any neurotransmitter is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that show a subset of the compounds of formula I, wherein X = S, S=O, or $(S=O)_2$, having the ability to regulate

the synthesis, storage, release, metabolism, reabsorption or receptor binding of any biogenic amine or any neurotransmitter. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. Particularly, the specification teaches that dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine has a binding affinity to 5-HT_{2a} and 5-HT_{2C} (see page 28, lines 6-7). The specification also teaches that "compounds" have a binding affinity to the alpha1 receptor, and that “compounds having a IC_{50} and K_i values lower than 1μM were considered active (see page 29, line 1-2). The specification does not provide any of the specific compounds which exhibit these effects. Due to the numerous compounds that could have been tested, as evidenced by the restriction requirement, it is not clear if compounds wherein X = S, S=O, or $(S=O)_2$ exhibited effective binding that met the active requirements.

(7) The quantity of experimentation necessary:

The instant claims read on any compound of formula I wherein X = S, S=O, or $(S=O)_2$ having the ability to regulate the synthesis, storage, release, metabolism, reabsorption or receptor binding of any biogenic amine or any neurotransmitter. As discussed above the specification fails to provide any support for the above activities. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every one of compounds as claimed, or at least a subset that is sufficiently representative of the compounds, to determine separately, as demonstrated by Wikstrom et al., which compounds regulated the synthesis, storage release, metabolism, reabsorption or receptor binding or each biogenic amine (i.e. serotonin, dopamine, norepinephrine) or neurotransmitter. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each compound having the above activity for the treatment of that particular disease, damage or disorder, in order to be able to fully carry out the invention commensurate in scope with the claims.

Genetech, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for the compound dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, but not for any compound of formula I wherein X = S, S=O, or $(S=O)_2$ to regulate the synthesis, storage, release, metabolism, reabsorption or receptor binding of any biogenic amine or any neurotransmitter.

4) Claims 1 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling the compound of formula I

wherein X = S, S=O, or $(S=O)_2$ and pharmaceutically acceptable salt, does not reasonably provide enablement for the solvates of the compounds of formula I wherein X = S, S=O, or $(S=O)_2$.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering a compound of formula I, wherein X = S, S=O, or $(S=O)_2$ pharmaceutically acceptable salts or solvates thereof. The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention:

The claim 1 is drawn to "a method of treating a disease damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter comprising administering to a subject in need thereof a compound of formula I....and pharmaceutical acceptable salt or solvate therof."

(2) The breadth of the claims:

Claims 1 and 12-15 embrace all forms of salts and solvates of the compound of formula I to treat a disease, damage or disorder of the central nervous system associated with a disorder of neurochemical equilibrium of a biogenic amine or other neurotransmitter The specification does not enable any (or a good subset) of the compounds of formula I, wherein X = S, S=O, or $(S=O)_2$, particularly the solvates to treat any central nervous system.

(3) The state of the prior art:

The state of the art regarding effectively treating any disease, damage or disorder of the central nervous system with solvates of the compounds of formula I is very low. For instance, Wikstrom et al. (US 5,288,748) teach that the compounds of formula I, which bind to 5-HT_{1A} (serotonin), D2 (dopamine) and NA alpha-2 (noradrenaline receptors treat depression (see columns 7 and 8 in its entirety and

claims 15 and 16). Particularly, compounds of the same core structure or even different diastereomers of the same compound have different if any activity towards the synthesis of DA and 5HT at the serotonin, dopamine and noradrenaline receptors (see Table 1). For instance compound (+)13a and (-)13a both showed activity at the D2 and 5HT1A receptor, but (-)13a did not effect the synthesis of DA or 5-HT. Thus, it can not be expected that all compounds with a similar core structure will have the same activity. Further, it can not be expected that just because a compound effects the synthesis of a bogenic amine does not mean that it will be effective in treating the disease or disorder. Kelly (Neurosciences, 1995, vol. 7, pp. 371-373) teaches that 5-Ht's have different roles in the central nervous system (see title). The operational properties of the 5-HT receptor on the neurons is determined by the receptor subtype, in which 5-HT has several (see page 372, column 1, paragraph 2, lines 1-15; and page 371, column 2, serotonin receptor family). Further, the synthesis of the solvates of each compound of formula I, wherein X = S, S=O, or $(S=O)_2$ is not known.

(4) The predictability or unpredictability of the art:

The predictability of effectively treating any disease, damage or disorder of the central nervous system with solvates of the compounds of formula I, wherein X = S, S=O, or $(S=O)_2$, is relatively low. Therefore, to one skilled in the art, treating any central nervous system disease, damage or disorder is unpredictable. In other words, just because there are potential to treat a central nervous system disorder, disease or

damage with a solvate of formula effective treatment has yet to be completely established. Therefore, because there is a "potential", it is unpredictable.

(5) The relative skill of those in the art:

The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts, as evidenced by Wikstrom et al. and Kelly.

(6) The amount of direction or guidance presented / working examples:

In the instant case, the guidance of the specification as to any solvates of the compound of formula I wherein X = S, S=O, or $(S=O)_2$ being able to treat any disease, damage or disorder of the central nervous system disorder, disease or damage is completely lacking. The specification as filed does not speak on or show any working examples any studies performed that show a subset of the solvates of the compounds of formula I, wherein X = S, S=O, or $(S=O)_2$, being able to having the ability to treat any disease, damage or disorder of the central nervous system. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.02. Particularly, the specification teaches that dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine has a binding affinity to 5-HT_{2a} and 5-HT_{2C} (see page 28, lines 6-7). The specification also teaches that "compounds" or “substance” reduced the immobility of animals (see page 29, paragraph 4 and page 30, paragraph 2), reduced amphetamine-induced

hyperlocomotion in animals (see page 30, last paragraph), reduced the effects of m-CPP, (see page 31, paragraph 3), reduced the period of agitation, convulsions and tremors in animals (see page 32, paragraph 3). The specification also teaches that "compounds" have a binding affinity to the alpha1 receptor, and that "compounds having a IC_{50} and K_i values lower than 1μM were considered active (see page 29, lines 1-2). The specification does not provide any of the specific compounds which exhibit these effects. Due to the numerous compounds that could have been tested, as evidenced by the restriction requirement, it is not clear if compounds wherein X = S, S=O, or $(S=O)_2$ nor solvates exhibited effective treatment and or binding.

(7) The quantity of experimentation necessary:

The instant claims read on <u>any</u> solvate of the compound of formula I wherein X = S, S=O, or $(S=O)_2$ being able to treat any disease, damage or disorder of the central nervous system. As discussed above the specification fails to provide any support for the above compounds being effective. Applicant fails to provide any information sufficient to practice the claimed invention, absent undue experimentation.

Particularly, the skilled practitioner would have to test each and every one of the solvates of the compounds as claimed, or at least a subset that is sufficiently representative of the compounds, to determine <u>treatment efficacy</u> for each condition. First, the practitioner would have to make the solvate, in which no guidance was given in the specification. Further, to test for treatment of the disease, a particular solvate

having the activity to effect the equilibrium of a biogenic amine or other neurotransmitters, such as one of those corresponding to the solvate of formula I, would have to be selected, and a suitable animal model and dosage regimen (dose amount, frequency, route of administration) would also have to be selected. If efficacy of the drug did not result, the dosage regime would have to be varied, for example by changing the dosage amount or route of administration, until efficacy was achieved. If no animal model of a condition is available for testing, then toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the treatment of the condition was shown with the particular compound, then another compound having the same activity would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compounds as claimed for treating central nervous order disorders, the process would have to be repeated. Thus, the skilled artisan would have to undergo exhaustive studies to evaluate each compound having the above activity for the treatment of that particular disease, damage or disorder, in order to be able to fully carry out the invention commensurate in scope with the claims.

Genetech, 108 F. 3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimation of general ideas that may or may not be workable.

In conclusion, the applicant is enabled for the compound dimethyl-[2(1H-8-thia-1-aza-dibenzo[e,h]azulen-2-ylmethoxy)-ethyl]-amine and the pharmaceutically acceptable salts having a binding affinity to 5-HT_{2a} and 5-HT_{2C}, but not for any compound of formula I wherein X = S, S=O, or $(S=O)_2$, particularly the solvates to treat a central nervous system disorder, disease or damage.

Conclusion

No claims allowed. To overcome 35 U.S.C. 112 rejections, the Examiner advises the following: 1) amending the specification to remove the first definition of treatment which includes language of prevention; 2) amend claims 1-15 to the read on the elected group of compounds binding to the 5-HT_{2a} and 5-HT_{2C} receptors; and 3) further amend claims 1 and 15 to remove solvate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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